GS 9137

Drug Class: **Integrase Inhibitors**

Drug Description

GS 9137 is a low molecular weight, highly selective integrase inhibitor that shares the core structure of quinolone antibiotics. [1] Integrase inhibitors are a new class of antiretrovirals that interfere with HIV replication by blocking viral ability to integrate into human cell genetic material. [2]

HIV/AIDS-Related Uses

GS 9137 has shown in vitro activity against B and non-B subtypes of HIV-1. It is being studied in Phase II trials for the treatment of HIV-1 infection in treatment-naive and -experienced patients.[3] [4]

Pharmacology

GS 9137 is a modified quinolone antibiotic with potent activity against HIV-1 on in vitro assays. GS 9137 has the ability to bind magnesium cations. Integrase has a single binding site for magnesium, an ion required for strand transfer reactions and the assembly of integrase onto specific viral donor DNA. GS 9137 may be a selective inhibitor of the strand transfer process.[5] [6] GS 9137 retains antiretroviral activity against multiple-drug-resistant HIV-1 in vitro.[7]

A Phase I pharmacokinetics study using single oral doses of GS 9137 was conducted in 32 healthy volunteers. Six patients in each group received daily GS 9137 doses of 100, 200, 400, or 800 mg with food or 400 mg fasting. When administered with food, GS 9137 had a half-life of approximately three hours, compared with a fasting half-life of approximately six hours. The mean maximum plasma concentration (Cmax) achieved with food was 903 ng/ml (+/- 391 ng/ml); the mean area under the concentration-time curve (AUC) with food was 3,942 ng-hr/ml (+/- 1,072 ng-hr/ml). The mean Cmax in a fasted state was 264 ng/ml (+/- 78 ng/ml), and the mean fasting AUC was 1,451 ng-hr/ml (+/- 308 ng-hr/ml). Cmax was achieved by 0.5 to 4 hours post-dose. Both Cmax and AUC increased across escalating daily doses of 100 to 800 mg in a less than dose-proportional manner.[8]

A randomized, double-blind, placebo-controlled trial in 40 HIV-1 infected patients not currently receiving antiretrovirals evaluated the effects of GS 9137 with food for 10 days. The following dosages were studied: 200, 400, and 800 mg twice daily (BID); 800 mg once daily (QD); and 50 mg QD plus ritonavir 100 mg QD. In each dosage group, six patients received GS 9137 and two patients received placebo. All groups demonstrated significant antiviral activity compared with placebo. Viral load decreased 30-fold with 200 mg GS 9137 BID, 59-fold with 800 mg GS 9137 BID, ninefold with 800 mg GS 9137 QD, and 100-fold with 400 mg GS 9137 BID and with 50 mg GS 9137 QD plus ritonavir dosages.[9]

Adverse Events/Toxicity

In a single-blind, randomized, placebo-controlled trial, GS 9137 was safe and well tolerated in healthy volunteers; no Grade 3 or 4 adverse events occurred. One patient experienced mild anorexia, and one patient experienced increased liver enzyme levels; the problems in both patients resolved on their own.[10] A randomized, double-blind, placebo-controlled trial in HIV infected patients also reported only mild adverse effects, with no Grade 3 or 4 events.[11]

Drug and Food Interactions

GS 9137 displays additive to highly synergistic antiviral activity in vitro with the following antiretroviral medications: lamivudine, lamivudine/zidovudine, zidovudine, tenofovir, tenofovir/lamivudine, efavirenz, indinavir, and nelfinavir.[12]

The absorption of GS 9137 increased approximately threefold when administered with food in a Phase I study.[13]

Clinical Trials

For information on clinical trials that involve GS 9137, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: GS 9137 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[14]

Dosage Form: GS 9137 has been studied alone and in combination with low-dose ritonavir at doses of 200, 400, and 800 mg BID and 50 and 800 mg QD.[15] Phase II studies in treatment-experienced patients are evaluating once daily doses of 25, 50, and 125 mg in combination with ritonavir 100 mg.[16]

Chemistry

CAS Name:

Chemistry (cont.)

Molecular weight: 447.88[18]

Other Names

GS-9137[19]

JTK-303[20]

Further Reading

Sato M, Motomura T, Aramaki H, Matsuda T, Yamashita M, Ito Y, Kawakami H, Matsuaki Y, Watanabe W, Yamataka K, Ikeda S, Kodama E, Matsuoka M, Shinkai H. Novel HIV-1 Integrase Inhibitors Derived from Quinolone Antibiotics. J Med Chem 2006 Mar 9;49(5):1506-8.

Ritonavir-Boosted GS-9137 Vs. Ritonavir-Boosted Protease Inhibitor(s) in Combination With Background ART. Available at:

Further Reading (cont.)

Manufacturer Information

GS 9137
Gilead Sciences Inc
333 Lakeside Dr
Foster City, CA 94404
(800) 445-3235

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. J Med Chem - 2006 Mar;49(5):1506-8

2. Gilead Sciences - Gilead Announces Results from Phase I/II Study of Investigational HIV Integrase Inhibitor GS 9137 [press release], February 9, 2006. Available at: http://www.gilead.com/wt/sec/pr_815084. Accessed 03/21/06.

3. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

4. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 160LB.

5. J Med Chem - 2006 Mar;49(5):1506-8

6. Recent Patents on Anti-Infective Drug Disc - 2006;1:1-15

7. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

8. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 580.

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12. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

13. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 580.

14. Gilead Sciences - Gilead Announces Results from Phase I/II Study of Investigational HIV Integrase Inhibitor GS 9137 [press release], February 9, 2006. Available at: http://www.gilead.com/wt/sec/pr_815084. Accessed 03/21/06.

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16. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Abstract 160LB.

17. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

18. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

19. Conf Retroviruses Opportunistic Infect. - 13th, 2006. Poster 508.

20. Gilead Sciences - Gilead Announces the Advancement of HIV Integrase Inhibitor GS 9137 to a Phase II Clinical Trial [press release], Jan 9, 2006. Available at: http://www.gilead.com/wt/sec/pr_801963. Accessed 03/21/06.